

Review

Age-Related Change in Mobility: Perspectives From Life Course Epidemiology and Geroscience

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Abstract

Mobility is the most studied and most relevant physical ability affecting quality of life with strong prognostic value for disability and survival. Natural selection has built the “engine” of mobility with great robustness, redundancy, and functional reserve. Efficient patterns of mobility can be acquired during development even by children affected by severe impairments. Analogously, age-associated impairments in mobility-related physiological systems are compensated and overt limitations of mobility only occur when the severity can no longer be compensated. Mobility loss in older persons usually results from multiple impairments in the central nervous system, muscles, joints, and energetic and sensory physiological systems. Early preclinical changes in these physiological systems that precede mobility loss have been poorly studied. Peak performance, rate of decline, compensatory behaviors, or subclinical deterioration of physiological resources may cumulatively influence both timing of mobility loss and chances of recovery, but their role as risk factors has not been adequately characterized. Understanding the natural history of these early changes and intervening on them would likely be the most effective strategy to reduce the burden of disability in the population. For example, young women with low bone peak mass could be counseled to start strength resistance exercise to reduce their high risk of developing osteoporosis and fracture later in life. Expanding this approach to other physiological domains requires collecting and interpreting data from life course epidemiological studies, establishing normative measures of mobility, physical function, and physical activity, and connecting them with life course trajectories of the mobility-relevant physiological domains.

Keywords: Epidemiology—Geroscience—Mobility—Life course.

Geroscience aims to understand the fundamental mechanisms of aging in order to discover pathways that could be targeted to reduce risk of chronic diseases and promote healthy aging. Geroscience generally focuses on molecular and cellular biomarkers of aging in relation to healthspan (1). Seals and Melov make the convincing argument for the need to characterize the functional effects of the molecular and cellular pathways under investigation and connect them with evidence-based markers of physiological function at the whole organism level, for example, motor, vascular, cognitive, metabolic, or kidney function (2,3).

In this review, we extend Seals and Melov’s proposition in two ways. First, we argue that there is a natural hierarchy in functional measures, with mobility and cognitive function at the apex, supported

by underlying physiological systems. Second, we argue that mobility and cognitive function, the functioning of underlying physiological systems, and the molecular and cellular mechanisms on which they all depend should be studied across life, and indeed are shaped by exposures and experiences acting independently, cumulatively, and interactively throughout life. Healthy biological aging is about maximizing function during growth and development, and maintaining function and delaying decline for as long as possible (4). A better understanding of the dynamic nature of these processes requires that scientists break the boundaries between biology, medicine, and population science to take an integrated life course approach to the study of aging.

We illustrate our argument by focusing on mobility, presenting evidence to support its primacy as a “hallmark” of aging, describe

age-related changes in mobility across life, and the drivers and modifiers of these changes. A parallel article could and should be written for cognitive function, and the extent to which mobility and cognitive impairment dynamically unfold together across life and are driven by similar risk and protective factors needs more investigation (5).

Mobility is a Key Hallmark of Functional Aging

Over the last few decades, we have learned how to increase longevity in model organisms, in most cases through modulating nutrient sensing and metabolic pathways, either through genetic manipulation, dietary regimens, or drugs affecting specific molecular pathways (6). In some cases, the increase in longevity has been associated with an expansion of healthy lifespan although data on preservation of physical and cognitive function are still sparse due to challenges in measuring these functional outcomes comparably across species (7). Opportunities for the translation of evidence from animal models into clinical trials have so far proved limited though more work in this direction is currently ongoing (7,8).

Most of what we know about aging in humans comes from longitudinal studies that have characterized changes in physiological parameters in the late portion of life, and explored the multifaceted mechanisms by which aging leads to mobility disability and cognitive impairment, including sources of heterogeneity between individuals (9).

Recognizing that the health of older persons is best assessed through measures of physical and cognitive function rather than disease status is a major breakthrough in clinical and epidemiological research on aging over the last three decades (10). Slower walking speed (most commonly assessed using usual walking speed achieved during a timed walk test over a short distance) and other multisystem performance measures of physical function (such as the time taken to rise from a chair and sit down several times, or tests of balance) are consistently associated with poorer well-being and quality of life in old age, track overall health status, and predict adverse health outcomes, including rising multimorbidity, health care resource utilization, disability in activities of daily living, nursing home admission, and earlier mortality (11–16). Noteworthy, mobility disability is associated with mortality even in nonagenarians, a population where other risk factors lose their prognostic value (17). There is growing evidence that a faster rate of decline in walking speed is also associated with worse outcomes (18,19). Older people themselves value their mobility highly and they see its loss as a key disadvantage of aging (4).

Little of this wealth of scientific knowledge has been translated into effective recommendations toward the promotion of a healthy old age. We claim that translation would be facilitated by taking a life course approach to the disablement process and recognizing that while mobility loss only becomes evident in the later stages of life, its roots can only be understood in the context of life course epidemiology, “the study of long-term biological, behavioral, and psychosocial processes that link adult health and disease risk to physical or social exposures acting during gestation, childhood, adolescence, earlier in adult life, or across generations” (20,21). In recent years, life course epidemiology has increasingly focused on the natural history of function, usually at the multisystem or body system level, and its age-related change, to understand the drivers of lifelong health and healthy aging, gathering evidence from maturing birth cohort and historical cohort studies. The development of “omics” capabilities in these cohorts increasingly facilitate a life course approach to

biological and molecular mechanisms, such as epigenetic processes linking development and environmental exposure to adult health and function (22,23).

Age-Related Changes in Mobility

No one study has tracked mobility in individuals across all life stages. We analyzed longitudinal data from the InCHIANTI study at baseline, and 3-, 6-, 9-, and 14-year follow-up. Average rates of change in walking speed per year of aging were computed in men and women of different age groups and for differently challenging mobility tasks, namely, walking 4 m at usual and fast speed and walking 400 m as fast as possible. To address selective attrition, which was relatively small in the InCHIANTI study, rates of change were estimated using mixed effect models with inverse probability weighting. The results of this analysis are summarized in Figure 1, and statistics on average rates of change by sex and 5-year age-group are reported in Supplementary Tables 1–3. Incidentally, the statistics provided can be used to support sample size calculations of clinical trials aimed at attenuating walking speed decline or preventing mobility loss across the lifespan. The message conveyed by the results is clear: Decline in mobility with aging becomes evident early in adulthood only when challenging tasks are assessed. For example, although the rate of decline in the 400-m walking task is already evident in participants who entered the study at the age of 20–25 years, performance in the 4-m fast speed task only declines after the age 40–50 years, and performance in the 4-m usual speed is relatively stable up to the age of 65–70 years. These findings suggest that early decline in mobility is detectable and may guide strategies for prevention targeted to individuals and populations. Every clinician would agree that detecting and understanding the causes of high blood pressure in young- and middle-aged individuals is important because of the potential gain in health associated with successful prevention. Analogously, detecting significant decline in mobility early in life and possible underlying causes may help prevent the development of disability later in life.

In the following sections of this article, we build on the analyses described above by describing the published evidence on changes that occur in mobility in old age because that is where most knowledge lies, and then provide evidence that those changes are preannounced by changes that occur in midlife or even during development.

Older Age

On average, the rate of decline in walking speed and other measures of lower extremity performance accelerates over the seventh decade of life, starting sometime between the ages of 60–70 years, with an extremely heterogeneous time course across individuals (Figure 2). It is customary to describe the trajectory of mobility loss as a downslope curve that shows a steeper decline late in life. At the individual level, such a representation is misleading (Figure 3). In single persons, loss of mobility occurs when the ability to compensate for the cumulative effects of impairments is exhausted and normal daily life becomes a challenge. Thus, individual's trajectories of walking performance likely resemble hockey sticks with the longer portion representing the stability in middle age and the shorter portion the accelerated decline. Because data on walking performance are typically collected at low frequency, the collective effect of these J-shaped curves delineates the inverse exponential curves commonly reported. Identifying the critical time of accelerated mobility decline is essential to understand trajectories of disability and identify risk factors, and can be accomplished with change point models that

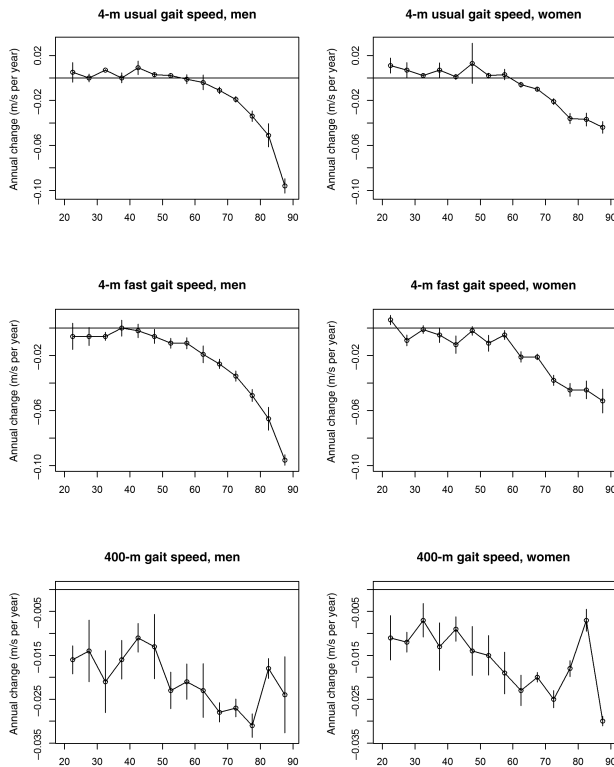


Figure 1. Average (and standard errors) annual rates of change of walking speed in men and women participants of the InCHIANTI study according to 5-year age groups at study entry. To address selective attrition, rates of change were estimated by mixed effect models with inverse probability weighting. Three different walking tasks were considered: 4-m walk at usual and fast speed and 400-m walk at fast speed. Rates of change were estimated using data from baseline and 3-, 6-, 9-, and 14-year follow-up. Rates are plotted at the lower age for the interval (eg, 20 is for participants who were 20–25 years old at study entry). Specific values plotted in this figure are reported in [Supplementary Tables 1a](#) and [b](#). Description of the performance measures assessed in InCHIANTI and a global description of the InCHIANTI study have been reported elsewhere ([134,135](#)).

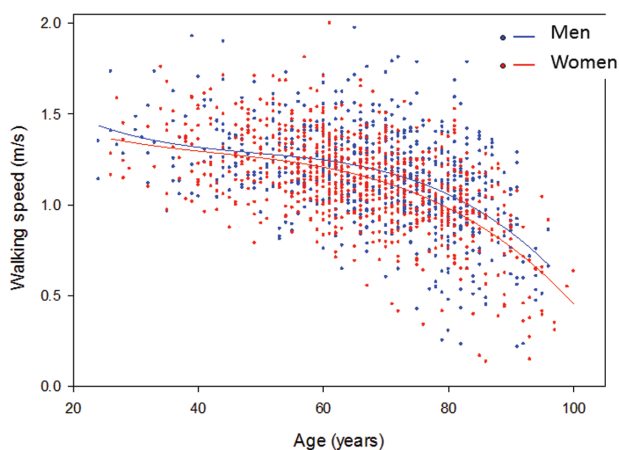


Figure 2. Usual walking speed at different ages in Men ($n = 711$) and Women ($n = 766$) participants of the Baltimore Longitudinal Study of Aging.

have already been applied to cognitive decline ([24](#)). However, fitting a trajectory for each individual that allows the identification of the point of change in slope will require more frequent measurements than are usually done in large epidemiological studies.

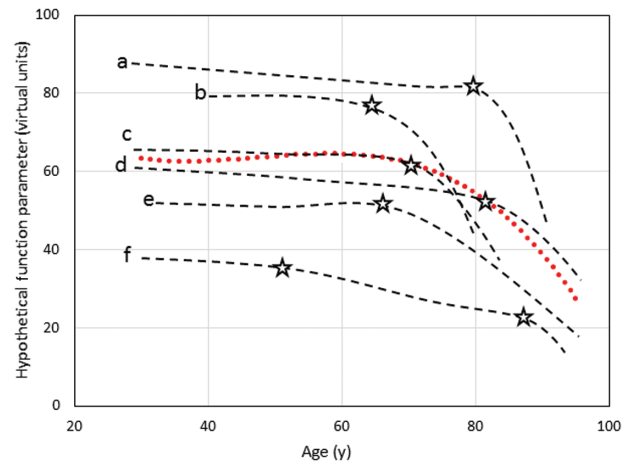


Figure 3. Hypothetical model of individual versus population trend. Trajectories a–f are from individual subjects, while the red line is the population overall trajectory. At the population level, the critical age for change appears to be around 70, but the ages when critical declines occur (as indicated by the stars) are quite variable across individuals.

Young-to-Middle Age

Performance in more challenging tasks of mobility, such as walking fast and for long distances, peaks sometime in the second decade, with large variability between individuals, depending on height, habitus, physical activity, and health status, the latter of which at this age tends to be relatively good in all but a few. Peak physical performance on other parameters is also observed in this phase of life. What happens afterwards depends on what parameter is considered. *Walking speed at usual pace* declines only slightly through to the sixth decade; the apparent stability of usual pace walking speed during most of adulthood hides substantial changes that occur in physiology that can still be compensated, and therefore do not manifest in overt functional changes. For example, a substantial reduction of fitness or nerve conduction velocity may occur before any limitation of mobility is perceived in daily life activities because of an abundance of reserve in early-to-mid life. When more challenging mobility tests are used, limitations emerge much earlier than the sixth decade ([Figure 1](#)). For example, in InCHIANTI study participants, the addition of challenges (ie, long distance or obstacles) revealed age-related differences in the young-to-middle age range that were not evident for usual pace walking tasks ([25](#)). This is consistent with data on maximum running time for 5000 m reported in the literature that show a progressively longer time to complete the race with aging from age 40 years onwards, both in men and in women which accelerates after age 60 ([Figure 4](#)). The interfering effect of challenges is not limited to the physical realm. There are considerable data showing that superimposing a cognitive task on to a walking task is followed by a substantial decline in walking performance and the effect size of such reduction increases with age and is probably already evident in middle age, but longitudinal trajectories of dual task performance have not been described ([26](#)).

Developmental Age

The ability to walk develops very early in life and marks a critical milestone in development and central nervous system maturation. Retardation of walking “the first step” of even a few months is considered an indicator of developmental delay that requires medical attention and can be the first sign of neurological or musculo-skeletal diseases ([27](#)). The signaling sequences, reflexes, integrative

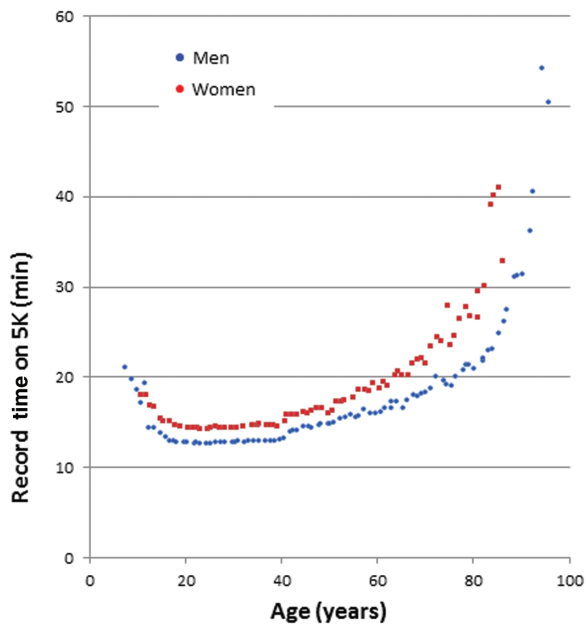


Figure 4. World record times for running 5,000 m according to age and sex.

inputs, and force-generating tissues necessary to build an efficient gait pattern are already present at or soon after birth. However, these intrinsic tools are matched to environmental cues and available motor resources to build the most efficient gait pattern customized to every individual (28). Studies have shown that even in the presence of a severe impairment, such as low strength or localized neurological damage, there is considerable plasticity that allows residual resources to build a different but often similarly efficient gait pattern (29). Indeed, it is likely that such a high level of plasticity reflects the strong evolutionary advantage that bipedal stance provides to humans, which has led to the selection and conservation of a number of compensatory mechanisms aimed at minimizing the chance of losing the ability to walk. However, whether different developmental trajectories of mobility also affect mobility in late life as compensatory mechanisms become less effective remains an open question that could have substantial practical implications.

Drivers and Modifiers of Age-Related Changes in Mobility

The key aging phenotypes that underpin mobility and may act as compensatory mechanisms to promote peak performance and prevent mobility decline are body composition and strength, energetics, homeostatic (dys)regulation, and peripheral and central nervous system function (30). In general, we think about the continuous change in physiological variables that affect mobility as having a developmental growth phase, reaching a peak at some point in life, and then declining linearly or nonlinearly with aging. However, such an ideal trajectory is almost always perturbed by intervening health events, such as diseases and trauma, that may have both transient and long-term effects on the trajectory of function. For example, even an individual with robust mobility may lose the ability to walk because of a traumatic hip fracture while skiing. This individual will likely have full recovery although the healing process may affect the joint architecture and increase the chances of osteoarthritis later in life. Treatment for cancer may be successful but lead to accelerated aging (31). Chronic

infections may be controlled by chronic activation of the immune system but result in reduced ability to build an effective inflammatory response when a new stimulus is presented. McEwen and Wingfield called this longer-term adverse effect of healing processes as type 2 chronic allostatic load (32).

Taking a life course perspective to aging means understanding (i) how physiological dimensions important for mobility change across life and how they affect mobility performance at each life stage; (ii) to what extent any early or cumulative effects of the environment (physical and social) or behavior, or of development (physical, cognitive, and emotional) on mobility and its change are mediated through these aging phenotypes; and (iii) how intervening health events modulate longitudinal trajectories of mobility, including chances of recovery and long-term effects. Ultimately, understanding how an organism adapts to the environment during development, for example, in terms of physical structure, acquiring and processing information, providing energy to drive the system, and compensate for physiological losses should enhance understanding of age-related functional decline (33,34). An exhaustive review is beyond the scope of this article and cannot be done because important pieces of this puzzle have not been investigated. We draw mainly on our own studies in the Baltimore Longitudinal Study of Aging (BLSA) (35) and in the MRC National Survey of Health and Development (NSHD) to illustrate our approach and we hope to stimulate further research that eventually will provide the missing elements (36).

There is a growing epidemiological literature demonstrating that indicators of physical growth and maturation, neurodevelopment (such as motor milestones and cognitive ability), and early socioeconomic conditions are associated with physical performance from midlife onwards in NSHD and other cohorts (37–44). Associations with the early environment that are independent of the adult environment are clues that developmental mechanisms may be involved. Possible mediators of what has been termed the “biological embedding” of early adversity include neural structure and function, hypothalamic–pituitary–adrenal axis effects, inflammatory processes, and epigenetics (45). Most of these studies have only looked at physical performance at one point in time, but indicators of neurodevelopment have been associated recently with midlife change in chair rise performance (46). Across adult life, there is evidence that cumulative exposure to physical activity, smoking, and other behavioral risk factors are associated with physical performance and its change from midlife onwards (47–55).

Body Composition and Strength

During development, any addition of muscle mass is followed very tightly by a predictable increase in strength as the new muscle tissue has good biomechanical quality, that is, generates a normal amount of strength per unit of mass. Muscle mass and strength peak on average during the third decade of life followed by a slow decline that accelerates sometime between 60 and 70 years of age especially in men (56–58). With age, the correlation between dual energy X-ray absorptiometry measures of muscle mass and strength weakens, and considerable decline in strength may occur in the absence of any detectable decline in mass (59); although correlations may remain more stable if MRI-derived muscle mass is used (60). Aging is also associated with a progressive reduction of biomechanical muscle quality, which is usually operationalized as the ratio between strength and mass (61).

Low muscle strength (but less consistently low muscle mass), as well as excessive and long-term adiposity, are risk factors for age-related mobility loss (62–64). Both muscle strength and adiposity are associated with factors from early life onwards and

intergenerationally. For example, the consistent positive association of birth weight with adult muscle strength, independent of later body size, suggests the long-term impact of intrauterine exposures (37,65). That adverse childhood socioeconomic conditions, independent of adult conditions, are associated with greater adult obesity and its age-related change, lower muscle mass, and strength suggests that early exposures leave long-term biological imprints on adult body composition (38,66–68).

A number of studies have shown that usual walking speed is correlated with strength only below a certain threshold level of strength. This is because in the absence of other coimpairments or special challenges, the amount of strength necessary for walking is minimal. In healthy individuals with “normal muscle strength,” it is unlikely that strength is a major contributor to any type of mobility limitation. Muscle related mobility loss only emerges when strength has declined below a critical threshold. However, even in midlife, a small proportion of the general population fall below this threshold and show subsequent mobility limitations (69).

Data from the Honolulu Heart Study described changes in grip strength over 27 years of follow-up in a sample who were 45–68 years old at baseline (70). The strong correlation between grip strength at baseline and follow-up suggests that those individuals who are weaker during midlife (even if still above a critical threshold) have a much lower reserve of strength in old age. Consistent with this interpretation, in the same cohort, baseline grip strength was highly predictive of functional limitations and disability 25 years later (71), a finding since replicated in other studies (72). The authors concluded that higher muscle strength in midlife protects people from old age disability by providing a greater safety margin above the threshold of disability.

Obesity is a major risk factor for mobility loss. Muscle mass is higher in obese individuals when compared with normal weight individuals because of the biomechanical stimulus provided by gravity (73,74). However, with rising body mass index, greater length of exposure to adiposity and reductions in the effectiveness of these compensatory mechanisms with aging (75), the increase in muscle mass for a given increase in fat mass is progressively lower than expected, therefore creating a discrepancy between the body mass that needs to be transported and the available “engine” (76). With increasing levels of obesity, there is also likely to be a greater mismatch between mass and strength (which may explain the inconsistent evidence of association between obesity and strength found in the literature) (62,74). The result of this is that with increasing obesity skeletal muscles are constantly working closer to their maximal capacity during antigravitational movements. Data from the BLSA and other studies suggest that the accumulation of adipose tissue plays an important role in the decline of muscle quality (61). This is consistent with recent NSHD findings that higher levels of weight gain from age 15 years onwards and earlier age at onset of obesity were both associated with increased odds of low muscle quality at the age of 60–64 years (73).

Energetics

Resting metabolic rate (RMR) normalized by body surface area or lean body mass is extremely high during the first year of life, between 50 and 60 cal/m²/h because of massive anabolic processes, especially protein synthesis that is energetically expensive (77). In childhood, RMR increases in parallel with increases in body mass due to linear growth, before reaching a plateau in adolescence (78), and then progressively declines across adulthood at least in part due to declines in fat free mass (79). Peak oxygen consumption declines with aging and

the rate of decline accelerates at older ages, as shown from longitudinal symptom limited treadmill test data collected in the BLSA (80).

To our knowledge, there have been no studies of the developmental origins of adult RMR and whether high RMR at younger ages is associated with different developmental steps. However, there have been some studies on cardiorespiratory fitness or aerobic capacity, the ability of the body to supply oxygen to skeletal muscles during sustained activity, as indicated by VO₂ max from maximal or submaximal exercise testing (81,82). Measures of size at birth were positively associated with cardiorespiratory fitness in British children (81); in adult life, the positive association was strongest for postnatal skeletal growth (40).

Aging is associated with a progressive decline in energetic efficiency so that performing the same task, for example, walking 10 m, becomes energetically more expensive as people age (83). The age-related declines in RMR are too small to offset the changes in aerobic capacity. The overall result of these energetic changes is that the window of energetic reserve, that is, the difference between maximum aerobic capacity and the amount of energy already committed to maintain life, progressively shrinks with aging. In most individuals, the energetic reserve is large enough to allow usual activity, with problems emerging only when the energetic demand becomes unusually high. However, in some individuals, even walking may induce an increased energetic demand that is challenging given the available reserve. These individuals respond by slowing down, therefore curtailing the instantaneous demand for energy (83). This hypothesis is consistent with data showing that although walking speed declines with aging, the instantaneous energetic cost of walking remains stable, and also with data showing that increased energetic cost of walking predicts future mobility decline (84,85). Thus, improving fitness even early in life could be an effective strategy to prevent disability in late life.

Homeostatic Dys/regulation

Animal and human research suggest that changes in the set point and the trajectories of hormonal systems are key mechanisms underlying the associations between early development and later adult function and disease risk, particularly those mediated through metabolic dysfunction (86,87). Neuroendocrine actions determine net energy availability, prioritizing resource allocation among growth, maintenance and reproduction, and regulating or modulating responses to contextual demands (88). For example, using data from NSHD, Bann and coworkers (67) demonstrated that lower socioeconomic conditions assessed across life were associated with hormonal states that have been associated with mobility performance in old age, namely, lower free testosterone among men, higher free testosterone among women, and lower insulin-like growth factor-1 (IGF-1) and higher evening cortisol in both sexes. There is evidence that age at menarche is affected by early-life factors, such as higher growth rate during childhood, better socioeconomic position, and a stressful family environment (89,90). In turn, earlier menarche is a risk factor for breast and endometrial cancer, metabolic syndrome, and gestational diabetes, perhaps because it is proxy measure measures of lifetime estrogen exposure (91–94). There is a long-term literature on the effects of the early environment on subsequent function of the hypothalamic–pituitary–adrenal axis, and cortisol in particular (88,95). Trade-offs in resource allocation that confer an early fitness advantage may have long-term costs on aging including functional decline (96). There is also a growing literature on the effects of the early environment on adult inflammatory markers; adverse socioeconomic and psychosocial environments being associated with a greater risk of proinflammatory states, which may be mediated through an increased risk of obesity (97,98).

In adult life, age-associated impairment of a number of homeostatic systems has been related to mobility decline (99). A complex multihormonal dysregulation characterized by an imbalance between catabolic and anabolic hormones occur with aging, which has important consequences for mobility and physical function (100). Connections between levels of androgens, estrogens, estradiol, IGF-1, and insulin across adulthood and characteristics of early life have been established, but more research on this topic is needed. Hormones implicated in glucose metabolism and soluble mediators of chronic, systemic inflammation have received the most attention and are particularly interesting because of their intrinsic pleiotropy, that is, capacity to influence multiple diseases and phenotypes (101,102). The strong relationship between prediabetes and diabetes with loss of mobility and other geriatric syndromes was described more than three decades ago. However, only recently have the multitude of mechanisms underlying this association been elucidated. Over the last 5 years, it has been shown that both diabetes and insulin resistance are associated with accelerated decline of muscle mass and strength with aging (103), perhaps because of muscle-specific energetic deficit due to lower mitochondrial number and function in persons with impaired carbohydrate metabolism (104). Two major microvascular complications of diabetes, peripheral neuropathy and retinopathy, may also affect mobility. In addition, individuals with diabetes tend to have vascular brain pathology, which is a major cause of gait impairment. The association between a mild chronic inflammatory state and mobility loss has been clearly established by many prospective studies (105,106).

Analogous to carbohydrate metabolism, inflammation may affect mobility through different mechanisms, including blocking anabolic pathways in muscle tissue, affecting tissue maintenance and repair, increasing the risk of anemia, and triggering an inflammatory reaction of the neuroglia and perhaps even the neurons (107). A recent line of research suggests that the proinflammatory state of aging may be due to the accumulation of senescent cells in multiple tissues and organs that acquire a "senescence associated proinflammatory phenotype" and contribute to reduced function across multiple tissues (108). A large literature has shown strong cross-sectional correlations of hormonal and nutritional parameters with walking performance. For example, circulating levels of several vitamins and antioxidant compounds, including flavonoids, tend to be lower in individuals with low walking speed, poor lower extremity performance, and self-reported mobility disability (109–112). Noteworthy, many of these associations have not been confirmed longitudinally and across studies, and in general, the assessment of nutritional status based on blood biomarkers has been limited to one or a few points in time. Thus, although there is rationale to believe that the quality of dietary intake will affect physical function and the conservation of mobility in old age, strong evidence for this association is lacking and this is a very active area of investigation.

Central and Peripheral Nervous System

Life course changes in the central and peripheral nervous systems, their development, maintenance, and decline likely show a similar trajectory to motor performance, rising rapidly to a peak at maturity in the third decade of life with a shallow midlife decline that then accelerates at older ages. Indeed, the dynamic interaction of cognitive and physical function has been a long-term scientific interest (5). There is also growing evidence of how normal variation in neonatal characteristics shape brain development, and how neurodevelopment and neurodegeneration are related. One hypothesis postulates

that the age-related decline in brain function mirrors developmental maturation, and it has been shown that the network of brain regions that develops relatively late in adolescence shows accelerated neurodegeneration (113,114). Childhood cognitive ability and educational attainment are strongly related to adult cognition although evidence for their effects on the onset and rate of cognitive decline remain inconsistent (115–118). A range of other social, psychological, and biological factors across life affect adult cognition (119); identifying those factors that predict onset and rate of decline has been more challenging. Adverse early conditions can induce changes in cognitive capacity and style (attention, memory, and learning), emotional regulation, and social relationships that threaten and erode future adult cognitive capacity and mental health that may impact on the decline of physical function (88).

Whether life course changes in the peripheral nervous system are affected by the environment and circumstances during infant and child development outside the context of specific diseases is unknown. Substantial changes in myelination and axonal growth occur during maturation, but their time course and functional effect on impulse conduction have not been studied. Aging is associated with loss of myelinated and unmyelinated nerve fibers, demyelination partially compensated by remyelination, axonal atrophy, which cause decline in nerve conduction velocity, muscle fibers denervation, impaired sensory discrimination, and altered autonomic responses (120). Some of these changes have been associated with muscle strength decline, mobility impairment, and disability (121–125). Aging also limits the capability for reinnervation and functional recovery after damage, such as trauma or compression, and makes the peripheral nervous system more susceptible to the effect of metabolic derangements such as diabetes. Interestingly, capabilities for axonal regeneration and reinnervation decline only late in life (120).

In adult life, the contribution of subclinical neuronal impairment to mobility disability, beyond the effect of overt neurodegenerative or neurovascular diseases has only recently been investigated partly because of the challenges of capturing relevant measures in large-scale populations. Prospective studies have found that the number of soft neurological signs is associated with walking speed and predicts falls (126). Few studies have examined covariation between cognition and physical function longitudinally (5). At the neuromuscular interface, a number of studies have suggested that the number of motor-neurons in the spinal cord declines with aging, starting as early as 35 years of age. However, neuronal loss has little or no functional consequences because the resulting denervation is normally compensated by parallel reinnervation although this compensatory mechanism becomes less effective with aging (127). It has been postulated that dysfunction of the central nervous system is the most frequent cause of mobility impairment in older persons, leading to slow movement, balance instability, and gait variability. Most studies have focused on dysfunction that occurs after acute brain damage, such as stroke, tumor, or head trauma. However, evidence is surfacing that subtle changes in the brain and peripheral nervous system that occur with aging and are not associated with overt symptoms can also affect gait performance and in some individuals contribute to mobility loss (122,126). A number of studies have connected cortical atrophy in specific brain regions with gait performance, including gait variability and gait speed (128). The association becomes even stronger for walking tests that include a strong cognitive component such as talking while walking or other dual tasks. Researchers have suggested that gait variability is an early biomarker of gait impairment independent and more precocious than slow walking speed, and particularly sensitive to neurological problems (129). That

neuropathology may affect walking performance and contribute to mobility loss is also suggested by data showing that the appearance of gait impairments is a strong risk factor for cognitive decline and dementia, suggesting that in some individuals motor and cognitive disorders may share the same pathologic background (130).

Strength and neuroplasticity are the two main compensatory mechanisms aimed at maintaining mobility in critical conditions. In frail older women with good balance, lower extremity strength is poorly correlated and poorly predictive of mobility disability (131,132), whereas the correlation and predictivity are high in those with poor balance, suggesting that excess strength reserve may compensate for poor balance. Whether interventions that increase strength may prevent or delay the progression to mobility loss is an important but still unanswered question.

A Life Course Model for Mobility Loss With Aging and the Promotion of Healthy Aging

From a public health perspective, addressing all major risk factors for mobility decline in order to promote independence in aging would be the ideal approach, but perhaps not the most parsimonious. Because we know that rates of decline in function of different physiological systems important for mobility are highly heterogeneous, an alternative and more parsimonious approach to mobility loss prevention is to identify the weakest system early in life, namely, the physiological system that appears to be most problematic for each individual. Then, we could target these physiological domains by highly focused, aggressive interventions. This proposition makes the assumption that those physiological parameters that show less functional reserve will most strongly contribute to mobility loss late in life in spite of intervening disease, and targeting them may result in effective prevention.

One conceptual issue that needs to be addressed is the dichotomy between the global effect of aging across the many physiological systems that leads to reduced functional reserve and, system specific susceptibility that differs between individuals because of their genetic, developmental and lifetime behavioral, and environmental characteristics. Functional reserve is the overall ability to compensate for the adverse effects of impairments, or recover from acute challenges to prevent functional loss in normal life. In the literature, this concept of functional reserve has also been termed stress response, homeostatic capacity, or resiliency. Relative weakness of some physiological functions early in life may not surface during clinical observation because they are fully compensated. However, they likely imply a high risk of functional consequences later in life when the ability to compensate is diminished because of aging. For example, individuals in whom the early impairment is a defect in energetics, will develop energetic-related mobility loss when functional reserve declines below a certain threshold. Thus, specifically addressing mitochondrial function early in life could be the best chance to prevent mobility loss. Our knowledge of how to modify these pathways is continually being strengthened. For example, there is observational evidence that inflammation can be changed by exercise and small pharmacological trials are being designed as a proof of principle (133). This approach of increasing the range of modifiable targets does not negate the traditional recommendations for aging well (of not smoking, eating healthily, being physically active, etc.). Nor do we deny that intervening on acute and chronic health events may substantially change the trajectory of mobility loss. We simply want to demonstrate that physiologic characteristics of early life, aging, and intervening health

conditions have cumulative and interactive effects over a long time period that shape the trajectory of mobility loss with aging. Whether intervening early on subclinical impairment can prevent mobility loss and perhaps also strengthen resiliency against the effect of diseases should be empirically tested.

This empirical validation can only be done in the context of longitudinal, and ideally life course, studies. Provocative tests, which challenge specific physiological systems, should be developed that can capture the severity of specific impairments at times when they remain fully compensated and do not cause mobility problems. Then, we need to test whether these subclinical impairments predict mobility loss with aging. Large-scale intervention studies should be implemented to demonstrate that intervening on the most severe, but still subclinical impairment can prevent mobility loss later in life. We recognize the scope and magnitude of such a study. In part, these hypotheses could be tested with available cohort resources, and through combining data across these cohorts, but ultimately, the implementation of large studies specifically customized for this purpose would provide the strongest answer.

Future Perspective: Integrating Geroscience and Life Course Epidemiology

In the discussion above, we purposely ignored the molecular and cellular mechanisms that promote peak functional reserve and then cause its decline with age, and the considerable heterogeneity of the rate of such decline across individuals. We need to integrate geroscience with life course epidemiology to discover the cause of physiological decline and loss of resiliency. Historically, the deterioration of functional reserve with age was considered a nuance in the causal pathway to deteriorating health, a covariate that had to be dealt with by statistical adjustment. More recently, the biological mechanisms of aging are unraveling, at least in animal models, and in time may explain how earlier environment and development impact functional aging and health span. For example, studies in mice have recently demonstrated that eliminating naturally occurring senescent cells improves lifespan and may also impact health span. These studies create the expectation that functional aging and health span will be increasingly modifiable leading to considerable improvement of population and individual health, delaying mobility loss and disability onset, and providing highly needed relief from the burden on health care expenditure of global population aging.

Supplementary Material

Supplementary material can be found at: <http://biomedgerontology.oxfordjournals.org/>

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